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ORIGINAL SCIENTIFIC REPORT

Effect of High Postoperative Body Temperature on Long-Term Prognosis in Patients with Gastric Cancer After Radical Resection

Hua-Long Zheng[1,2,3,4] · Jun Lu[1,2,3,4] · Ping Li[1,2,3,4,] · Jian-Wei Xie[1,2,3,4] · Jia-Bin Wang[1,2,3,4] · Jian-Xian Lin[1,2,3,4] · Qi-Yue Chen[1,2,3,4] · Long-Long Cao[1,2,3,4] · Mi Lin[1,2,3,4] · Ru-Hong Tu[1,2,3,4] · Ze-Ning Huang[1,2,3,4] · Ju-Li Lin[1,2,3,4] · Chao-Hui Zheng[1,2,3,4] · Chang-Ming Huang[1,2,3,4]

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Abstract

Background There is a lack of data on the effect of high postoperative body temperature on disease-free survival (DFS) in patients who underwent radical gastrectomy.

Methods Patients who underwent radical gastrectomy from January 2006 to December 2011 were selected. The highest body temperature within 1 week after operation was used to establish diagnostic thresholds for high and low body temperature through X-tile software.

Results A total of 1396 patients were included in the analysis. The diagnostic threshold for high body temperature was defined as 38 °C; 370 patients were allocated to the high-temperature group (HTG), while another 1026 patients were allocated to the low-temperature group (LTG). For all patients, survival analysis showed that 5-year DFS in the HTG was significantly lower than that for the LTG (55.6% vs 63.9%, $P = 0.007$). Multivariate analysis revealed that high postoperative body temperature was an independent prognostic risk factor for 5-year DFS (HR = 1.288 (1.067–1.555), $P = 0.008$). For patients without complications, survival analysis showed that the 5-year DFS rate in the HTG was lower than that for the LTG (57.5% vs 64.4%, $P = 0.051$), especially in patients with stage III gastric cancer (31.3% vs 41.7%, $P = 0.037$). For patients with complications or infectious complications, there were no significant differences between the HTG and LTG regarding 5-year DFS (49.3% vs 58.2%, $P = 0.23$ and 49.4% vs 55.1%, $P = 0.481$, respectively).

Conclusion For stage III gastric cancer patients without complications, high postoperative body temperature can significantly reduce the 5-year DFS. These patients may benefit from more aggressive adjuvant therapy and post-operative surveillance regimens.

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Hua-Long Zheng and Jun Lu have contributed equally to this work and should be considered co-first authors.

✉ Ping Li
24627878@qq.com

✉ Chao-Hui Zheng
wwkzch@163.com

✉ Chang-Ming Huang
hcmlr2002@163.com

[1] Department of Gastric Surgery, Fujian Medical University Union Hospital, No. 29 Xinquan Road, Fuzhou 350001, Fujian Province, China

[2] Department of General Surgery, Fujian Medical University Union Hospital, Fuzhou, Fujian Province, China

[3] Key Laboratory of Ministry of Education of Gastrointestinal Cancer, Fujian Medical University, Fuzhou, Fujian Province, China

[4] Fujian Key Laboratory of Tumor Microbiology, Fujian Medical University, Fuzhou, Fujian Province, China

Introduction

Gastric cancer is the fifth most common tumor in the world and is ranked as the third most common cause of tumor-related death [1]. The prevalence of stomach cancer is more common in Far East countries, such as Japan, South Korea, and China, than those in the West [2]. Radical gastrectomy is the only effective method to cure gastric cancer [3, 4]. However, even after R0 resection, a considerable number of patients recur, especially those with advanced gastric cancer [5–7]. Tumor infiltration depth and lymph node metastasis are recognized as independent risk factors for prognosis in gastric cancer patients [3, 4, 8, 9]. In addition, a large number of studies have shown that postoperative complications are independent risk factors for long-term survival, such as gastric cancer, colorectal cancer, esophageal cancer, and gastric esophageal cancer [10–13]. Artinyan et al. [14] demonstrated that postoperative complications after colorectal cancer resection, especially infectious complications, were risk factors for long-term survival in addition to disease and treatment factors. Tokunaga et al. [10] demonstrated that postoperative abdominal infection was a poor prognostic factor for overall survival and disease-free survival in patients with gastric cancer.

Body temperature is a sensitive indicator for whether the internal environment of the body is in a stable state. Body temperature generally changes after an operation, primarily through increased body temperature as fever. According to the definition of postoperative hyperthermia, the incidence rate ranges between 29 and 75% [15–17]. Postoperative fever is a common and potentially serious disease. Postoperative fever may indicate the presence of an infected site or severe complications; however, in most cases, fever is the result of noninfectious causes [18]. Studies have shown that approximately 90% of postoperative fever is due to noninfectious causes. White blood cell count, blood sedimentation, CRP, urine culture, blood culture, and chest radiograph can be used to identify the cause of fever [15, 19, 20]. A large number of studies have demonstrated the relationship between postoperative complications and long-term prognosis [10–14]. However, as a sensitive index, the impact of postoperative fever, especially those with no clinical evidence of infectious complications, on long-term prognosis has not yet been reported. The purpose of this study was to investigate the effect of high body temperature on disease-free survival in patients after radical gastrectomy.

Materials and methods

Case inclusion and general information

A retrospective review was performed using a prospectively maintained gastric cancer database at The Affiliated Hospital of Fujian Medical University following institutional review board approval. We initially examined 1974 patients with gastric adenocarcinoma from January 2006 to December 2011. Patients who underwent exploration biopsy, palliative surgery, diagnosed residual stomach cancer, had synchronous other malignancies within 5 years or experienced postoperative death within 90 days were excluded. Ultimately, a total of 1396 patients were included in the analysis. The type of surgical resection and the extent of lymph node dissection were selected according to the Japanese gastric cancer treatment guidelines [21]. Cancer staging was based on the 7th edition of the Union for International Cancer Control (UICC) TNM classification system [22]. After surgery, most patients with stage II or higher cancer received postoperative adjuvant chemotherapy with 5-fluorouracil-based regimens. The proportion of patients in the high temperature group with stages II–III gastric cancer receiving adjuvant chemotherapy was 59.1% (162/274), while the proportion of patients in the low temperature group was 60.6% (442/729). Patients were followed up every 3 months for a 2-year period and then every 6 months for 3–5 years postoperation. The final follow-up evaluation was conducted in June 2017. The ratio of censored cases within 5 years was 14.8% (206/1396). The median follow-up time of living patients was 68 months. Most routine follow-up appointments included a physical examination, laboratory tests (including CA19-9, CA72-4, and CEA level measurements), chest radiography, and abdominopelvic ultrasonography or computed tomography, along with an annual endoscopic examination. A total of 479 (91.2%) patients died of gastric cancer, and 46 (8.8%) patients died of other cause.

The definition of temperature

A mercury thermometer was used every 4 h to measure the axillary temperature for 7 days after surgery. Basal body temperature (BBT, measured at 6 am) and the maximum body temperature (MBT, maximum daily armpit temperature) were used to select the highest temperature over 7 days to analyze the postoperative temperature of the patient. According to the 5-year disease-free survival data, we used X-tile software (http://www.tissuearray.org/rimmlab/) to obtain the smallest P values of the log-rank $\times 2$ test and determine the diagnostic threshold for high body

temperature. A temperature above the diagnostic threshold was defined as a high body temperature. When the temperature value was 38.1 °C, the ×2 corresponding values from X-tile achieved a maximum of 7.72 ($P = 0.006$). For convenient clinical application, a highest temperature of ≥38 °C was defined as a high temperature (HT) within a week, while <38 °C was defined as a low temperature (LT) (Fig. 1).

Definition of postoperative complications

The definition for each complication is based on the literature [23–30]. Surgical complications included abdominal infection, anastomotic leakage, intestinal obstruction, gastroparesis, incision-related complications, intra-abdominal bleeding, ileus, pancreatic fistulas, pancreatitis reflux esophagitis, malabsorption, and dumping syndrome. Non-surgical complications include pulmonary, urinary, renal, hepatic, cardiac, and endocrine complications. Mortality was defined as any death that occurred during the hospital stay. Infectious complications were defined as pneumonia, urinary tract infection, or any surgical site infection (superficial, deep, and/or organ space) [14]. Complications were classified according to the modified version of the Clavien–Dindo classification system reported by Dindo et al. [31]. The morbidity C–D grade II or higher was analyzed, and patients with complications of less than grade II were considered no complication. When two or more complications occurred in one patient, the higher grade was adopted [32]. Complications higher than grade III were defined as "major" complications.

Statistical analysis

The primary outcome of interest was disease-free survival, which was defined as the time from the date of surgery to the date of recurrence or death. Tumor recurrence was confirmed by the radiologic or pathologic identification of either local recurrence or distant metastasis. To minimize the effect of early deaths resulting from postoperative complications, patients who died within 90 days of an operation were excluded from the survival analysis. In this study, X-tile plots were used as a new bioinformatics tool for biomarker assessment and outcome-based cutoff point optimization [33, 34]. All data were statistically processed with the Statistical Package for Social Sciences (SPSS), version 19.0 J, for Windows (SPSS Inc., Chicago, IL, USA). The continuous variables were represented by mean ± standard deviation. Categorical variables were analyzed with the Chi-square test or Fisher's exact test, whereas continuous variables were analyzed with the Student's t test. Survival curves were calculated using the Kaplan–Meier method, and differences between curves were analyzed using the log-rank test. The univariate and multivariate hazard ratios were calculated using a COX proportional hazard model. All significant variables in the univariate analysis were entered into a multivariate analysis. Differences were considered statistically significant when $P < 0.05$. Confidence intervals (CIs) were calculated at the 95% level.

Results

Clinicopathologic characteristics

Based on the definition of postoperative high body temperature (≥38 °C), 370 patients matched the diagnostic criteria and were allocated to the high-temperature group (HTG), while another 1026 patients were allocated to the low-temperature group (LTG). There were no statistically significant differences observed for the clinicopathologic characteristics between the two groups of patients, including in age, sex, tumor site, tumor size, site of recurrence, or postoperative stages. However, the incidence of overall complications (22.7% vs 8.5%, $P < 0.001$) and infectious complications (18.9% vs 5.1%, $P < 0.001$) was significantly higher versus the LTG (Table 1).

The effect of hyperthermia on 5-year disease-free survival in all patients

The HTG 5-year disease-free survival rate was significantly lower than that of the LTG (55.6% vs 63.9%, $P = 0.007$), and further stratified analysis showed that the differences in the 5-year disease-free survival rate between the two groups with stage I (90.3% vs 92.8%, $P = 0.451$) and stage II (73.1% vs 74.5%, $P = 0.877$) were not statistically significant. However, the 5-year disease-free survival rate for stage III in the HTG was significantly lower than that in the LTG (31.6% vs 41.8%, $P = 0.015$) (Fig. 2). Univariate and multivariate COX regression analysis showed that postoperative hyperthermia was an independent prognostic risk factor for 5-year disease-free survival (HR = 1.288 (1.067–1.555), $P = 0.008$) (Table 2).

The effect of hyperthermia in patients without complications

For patients with no complications, including 286 cases in the HTG and 939 cases in the LTG, the differences in the general clinicopathologic data of the two groups were not statistically significant (Supplementary Table 1). Survival analysis showed that the HTG 5-year disease-free survival rate was lower than that for the LTG (57.5% vs 64.4%, $P = 0.051$), and further stratified analysis showed that

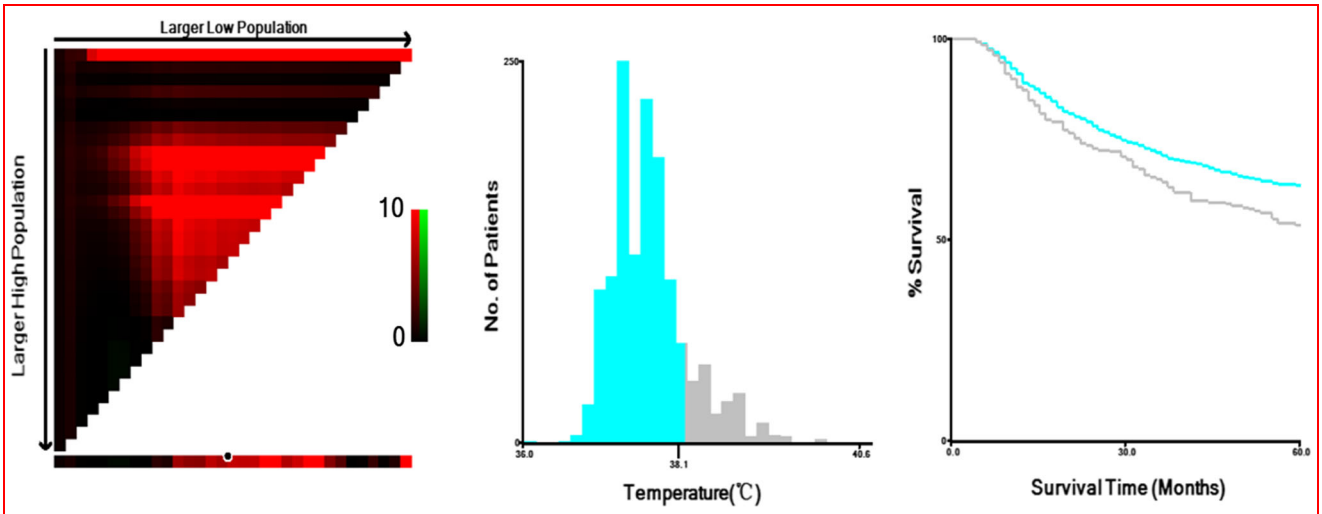

Fig. 1 Cutoff value of temperature for high temperature by X-tile software

patients with stage I (89% vs 93.7%, $P = 0.185$) and stage II (78% vs 76.4%, $P = 0.762$) did not have significantly different 5-year disease-free survival rates. However, for patients with stage III (31.3% vs 41.7%, $P = 0.037$), the HTG 5-year disease-free survival rate was significantly lower than that for the LTG (Fig. 3). Univariate and multivariate COX regression analyses were performed for patients with no complications, and high body temperature was an independent risk factor for 5-year disease-free survival (HR = 1.268 (1.027–1.565), $P = 0.027$) (Table 3). For stage III patients with no complications, further survival analysis revealed that the HTG 5-year overall survival rate (31.3% vs 42%, $P = 0.035$) and disease-specific survival (34.4% vs 44.9%, $P = 0.047$) were significantly lower than that for the LTG (Supplementary Fig. 1).

Hyperthermia has no obvious effect on 5-year disease-free survival in patients with complications

For patients with complications, with the exception of tumor location [HTG vs LTG, upper 22 (26.2%) vs 22 (26.2%), middle 8 (9.5%) vs 21 (24.1%), $P = 0.013$], there were no statistically significant differences in the clinicopathologic data between the HTG and LTG (Supplementary Table 2). Survival analysis showed that the 5-year disease-free survival rate difference (49.3% vs 58.2%, $P = 0.23$) between the HTG and LTG was not significant. Further stratified analysis showed that in patients with stage I (95% vs 83.3%, $P = 0.223$), stage II (50% vs 58.3%, $P = 0.561$), and stage III (32.2% vs 43%, $P = 0.354$), the 5-year disease-free survival rates were not significantly different between the two groups (Supplementary Fig. 2).

Hyperthermia has no obvious effect on 5-year disease-free survival in patients with infectious complications

For patients with infectious complications, differences in the clinicopathologic data between the HTG and LTG were not significant (Supplementary Table 3). Survival analysis showed that the 5-year disease-free survival rate between the HTG and LTG (49.4% vs 55.1%, $P = 0.481$) was not significant, and further stratified analysis showed that for stage I (93.3% vs 85.7%, $P = 0.481$), stage II (45.5% vs 58.3%, $P = 0.528$), and stage III (36.1% vs 37.3%, $P = 0.796$) patients, the 5-year disease-free survival rate difference between the two groups was not statistically significant (Supplementary Fig. 3).

Discussion

To meet the needs of normal activities, humans have a relatively constant body temperature. The relative stability of body temperature is regulated by the thermoregulation center. The body's endogenous and exogenous pyrogens can cause dysfunction of the thermoregulatory center. Exogenous pyrogens are usually microorganisms or their by-products, which induce fever by increasing the production of endogenous pyrogens. Endogenous pyrogens can be metabolites of the immune complex, complements, cytokines, or steroid hormones. These factors stimulate the release of prostaglandins, raise the temperature set point, and cause fever when body temperature rises beyond the normal range. Postoperative fever is a common clinical manifestation in patients with abdominal surgery. Tissue damage during the operation itself can cause the release of

Table 1 Clinicopathologic characteristics (total patients)

Characteristics	HT group (n = 370)	LT group (n = 1026)	P
Age (years)	60.85 ± 11.31	60.56 ± 11.28	0.674
Gender			
Male	279 (75.4%)	764 (74.5%)	0.721
Female	91 (24.6%)	262 (25.5%)	
BMI (kg/m^2)	22.44 ± 3.11	22.03 ± 3.58	0.06
Comorbidity			
Hypertension	90 (24.3%)	217 (21.2%)	0.206
Diabetes	37 (10.0%)	85 (8.3%)	0.317
Coronary heart disease	22 (5.9%)	54 (5.3%)	0.62
Arrhythmia	1 (0.3%)	5 (0.5%)	0.999
COPD	1 (0.3%)	3 (0.3%)	0.999
Hyperthyroidism	1 (0.3%)	7 (0.7%)	0.33
Hepatic	7 (1.9%)	10 (1.0%)	0.173
Renal disease	3 (0.8%)	10 (1.0%)	0.999
Tumor location			
U	96 (25.9%)	266 (25.9%)	0.423
M	49 (13.2%)	169 (16.5%)	
L	183 (49.5%)	493 (48.1%)	
≥2 areas	42 (11.4%)	98 (9.6%)	
Tumor size (mm)			
Vertical	47.55 ± 23.87	47.70 ± 26.32	0.922
Horizontal	40.25 ± 20.79	39.91 ± 22.03	0.799
HB (g/l)	130.16 ± 94.44	124.23 ± 25.47	0.237
pStage			
IA	72 (19.5%)	204 (19.9%)	0.587
IB	24 (6.5%)	93 (9.1%)	
IIA	34 (9.2%)	87 (8.5%)	
IIB	43 (11.6%)	141 (13.7%)	
IIIA	42 (11.4%)	113 (11.0%)	
IIIB	66 (17.8%)	157 (15.3%)	
IIIC	89 (24.1%)	231 (22.5%)	
Overall complications	84 (22.7%)	87 (8.5%)	<0.001
Major complications	23 (6.2%)	16 (1.6%)	<0.001
Infection-related complications	70 (18.9%)	52 (5.1%)	<0.001
Abdominal infection	16 (4.3%)	12 (1.2%)	<0.001
Anastomotic leakage	20 (5.4%)	5 (0.5%)	<0.001
Intra-abdominal bleeding	13 (3.5%)	11 (1.1%)	0.002
Intestinal obstruction	2 (0.5%)	5 (0.5%)	>0.999
Gastroparesis	7 (1.9%)	15 (1.5%)	0.569
Incision-related complications	9 (2.4%)	6 (0.6%)	0.006
Chylous leak	6 (1.6%)	6 (0.6%)	0.094
Pneumonia	99 (26.8%)	67 (6.5%)	<0.001
Dysfunction of liver	2 (0.5%)	1 (0.1%)	0.173
Cardio-cerebrovascular system	6 (1.6%)	7 (0.7%)	0.119
Urinary tract infection	0 (0.0%)	1 (0.1%)	>0.999
Site of recurrence			0.795
Peritoneum	48	118	
Liver	43	102	
Local/regional lymph nodes	39	93	
Others	18	29	
Unknown	13	28	

COPD chronic obstructive pulmonary disease

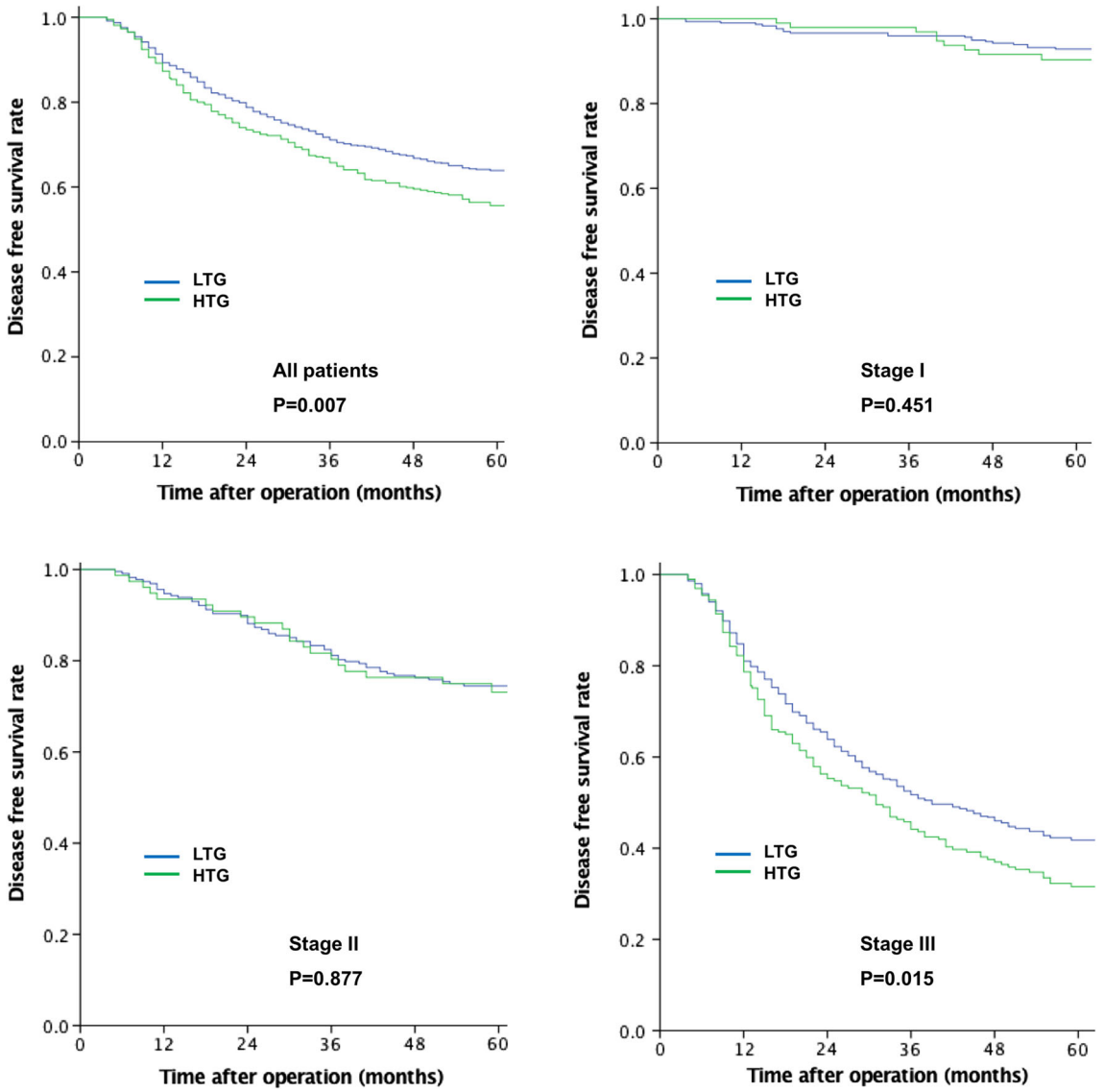

Fig. 2 5-Year disease-free survival: LTG versus HTG in all patients

endogenous pyrogens, such as interleukins, tumor necrosis factor, and others, causing fever [17, 19]. For medical staff, it is important to recognize that fever is only a sign of inflammation and not necessarily an infection.

Postoperative fever is a common clinical manifestation of infection. Our research showed that the high-temperature group had a significantly greater incidence of infectious complications compared to the low-temperature group (18.9% vs 5.1%, $P < 0.001$). Postoperative infectious complications are associated with decreased long-term survival and are independent of patient, disease, and treatment factors, particularly severe postoperative infections [10, 14]. Our study showed that the 5-year disease-free survival rate in the high-temperature group was significantly lower than that of the low-temperature group (55.6% vs 63.9%, $P = 0.007$). As a simple objective indicator, a high temperature indicates poor long-term prognosis after surgery.

Postoperative fever is a common and potentially serious disease, as it may indicate the presence of infection or severe complications; however, in most cases [18], there is no clinical evidence of infection in postoperative patients with a high body temperature. Fanning et al. [15] found no infectious evidence for 92% of postoperative fever patients. Our study showed that the proportion of hyperthermia patients with no clinical evidence of infectious complications was 77.3% (286/370). The analysis of patients with no clinical evidence of complications showed that the 5-year disease-free survival rate was lower than the LTG (57.5% vs 64.4%, $P = 0.051$), especially in patients with

Table 2 Univariate and multivariate cox regression analysis for disease-free survival (total patients)

Variable	Univariate analysis OR (95% CI)	*P*	Multivariate analysis OR (95% CI)	*P*
Gender				
Male versus female	1.02 (0.838–1.242)	0.843		
Age				
≥65 versus <65	1.487 (1.252–1.765)	<0.001	1.358 (1.141–1.616)	0.001
BMI				
≥25 versus <25	0.779 (0.607–1.001)	0.051		
Operation method				
TG versus SG	1.997 (1.676–2.379)	<0.001	1.426 (1.189–1.71)	<0.001
Pathology stage				
I + II versus III	0.72 (0.605–0.856)	<0.001	0.822 (0.69–0.979)	0.028
Temperature				
HG versus LG	1.29 (1.071–1.553)	0.007	1.288 (1.067–1.555)	0.008
Tumor size (mm)				
≥40 versus <40	4.455 (3.463–5.732)	<0.001	3.725 (2.872–4.833)	<0.001
Vascular/nerve/lymphatic invasion				
Yes versus no	1.257 (1.008–1.567)	0.042	1.132 (0.907–1.414)	0.273

TG total gastrectomy, *SG* subtotal gastrectomy

Table 3 Univariate and multivariate cox regression analysis for disease-free survival (no complication patients)

Variable	Univariate analysis OR (95% CI)	*P*	Multivariate analysis OR (95% CI)	*P*
Gender				
Male versus female	0.946 (0.753–1.188)	0.631		
Age				
≥65 versus <65	1.291 (1.047–1.593)	0.017	1.342 (1.111–1.62)	0.002
BMI				
≥25 versus <25	1.013 (0.759–1.353)	0.929		
Operation method				
TG versus SG	1.298 (1.045–1.612)	0.018	1.259 (1.034–1.534)	0.022
Pathology stage				
I + II versus III	0.163 (0.129–0.207)	<0.001	0.22 (0.17–0.286)	0.001
Temperature				
HG versus LG	1.278 (1.012–1.614)	0.04	1.268 (1.027–1.565)	0.027
Tumor size (mm)				
≥40 versus <40	2.092 (1.346–3.253)	0.001	1.77 (1.304–2.403)	0.003
Vascular/nerve/lymphatic invasion				
Yes versus no	1.075 (0.831–1.392)	0.582		
Chemotherapy				
Yes versus no	0.829 (0.674–1.02)	0.076		

TG total gastrectomy, *SG* subtotal gastrectomy

stage III gastric cancer (31.3% vs 41.7%, $P = 0.037$). Multivariate COX regression analysis showed that postoperative hyperthermia was an independent prognostic risk factor for patients with no complications of stage III gastric cancer (HR = 1.302 (1.031–1.646), $P = 0.027$).

The mechanism for how postoperative hyperthermia decreased the disease-free survival of patients who

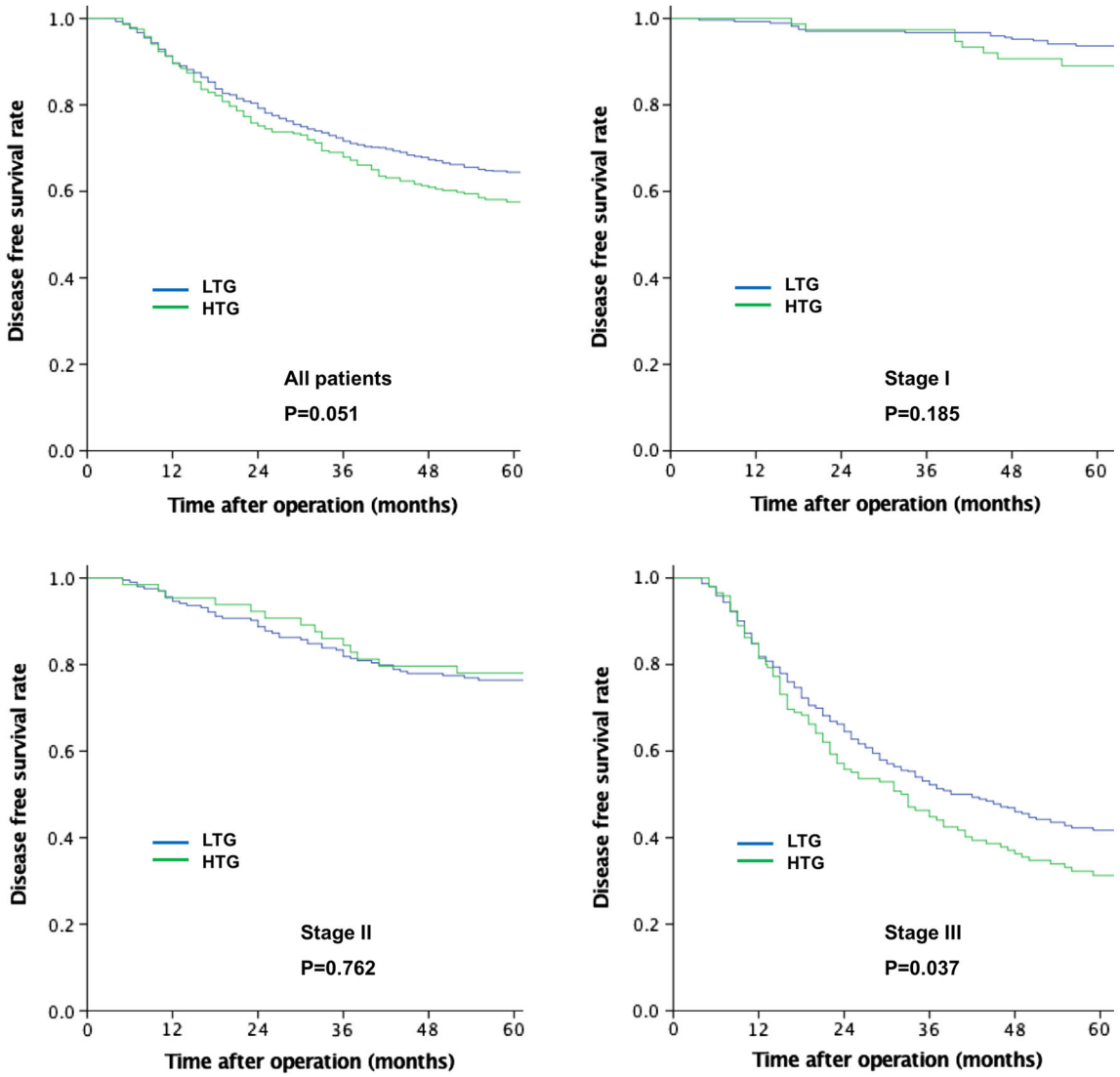

Fig. 3 5-Year disease-free survival: LTG versus HTG in patients with no complications

underwent radical gastrectomy is not clear, and there is a lack of clinical evidence proving the existence of infectious complications after an operation. The perioperative period, including anesthesia, blood loss, blood transfusion, postoperative pain, and other factors, can inhibit cellular immunity [35–45]. The degree of inhibition of postoperative cellular immunity was also related to the degree of surgical trauma and tissue injury [35]. Among the various secretions during the perioperative period, Goldfarb et al. reported that prostaglandins were the key substances involved in postoperative cellular immune suppression [46–48]. Wojtowicz-Praga et al. reported that cancer cells can suppress cellular immunity by secreting prostaglandins, thus escaping the destruction of the immune system [49, 50]. In vitro, prostaglandins have been repeatedly shown to directly inhibit the activity of NK cells and inhibit the secretion of the auxiliary type 1 (TH1) cytokines that are essential for the maintenance of cellular immunity. The increase in the postoperative body temperature set-point is regulated by prostaglandins; thus, we hypothesize that patients with stage III gastric cancer have greater trauma after surgery, which can cause increased secretion of high levels of prostaglandins, which then increase body temperature and inhibit cellular immunity and thus promote tumor transfer and early relapse.

There are several limitations to this study: (1) It was a single-center retrospective study, and thus its conclusions remain to be verified by external data or further multicenter prospective studies, (2) HTG is affected by usage of cooling agents, and so "CRP" may be a better surrogate [51], and (3) the effect of high body temperature on the immune system was not studied. Nevertheless, this study is

the first to assess the utility of postoperative hyperthermia in assessing the long-term curative effect on patients with gastric cancer, especially those without stage III gastric cancer complications.

In conclusion, as an easily accessed index, high postoperative body temperature is an independent prognostic risk factor for gastric adenocarcinoma patients. It is not enough to simply memorize that postoperative fever is a common clinical manifestation after operation; we need to pay more attention to postoperative fever. Based on our findings, strategies to prevent postoperative fever and implement more intensive surveillance protocols for those patients may improve long-term outcomes in patients undergoing radical gastrectomy.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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